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10/691,529	10/24/2003	Wei Liu	WYE-010	1341

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KIRKPATRICK & LOCKHART NICHOLSON GRAHAM LLP/WYETH
STATE STREET FINANCIAL CENTER
ONE LINCOLN STREET
BOSTON, MA 02111-2950

EXAMINER	
RAGHU, GANAPATHIRAM	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 08/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/691,529	LIU ET AL.	
	Examiner	Art Unit	
	Ganapathirama Raghu	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *9* is/are allowed.

6)☒ Claim(s) *8,10 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *SEQ ALIGN*.

DETAILED ACTION

Application Status

In response to the Office Action mailed on March 03, 2006, Applicants filed a response and amendment received on June 09, 2006. Said amendment, canceled claims 1-7, 12-23 and amended claims 8-11. Thus, claims 8-11 are pending in the instant Office Action.

Objections and rejections not reiterated from previous action are hereby withdrawn.

Withdrawn- Claim Rejections 35 USC § 112

Previous rejection of Claim 8 35 U.S.C. 112, second paragraph for as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the applicant's persuasive argument.

Withdrawn- Claim Rejections 35 USC § 112

Previous rejection of Claims 10-11 35 U.S.C. 112, second paragraph for as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the applicant's amendment of claims 10-11 and persuasive argument.

Claim Rejections 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8 and 10-11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 8 and 10-11 are directed to an isolated polypeptide comprising a fragment or variant of a fragment of SEQ ID NO: 2, wherein the said fragment includes at least 200 consecutive amino acid residues of SEQ ID NO: 2 and wherein the variant and the said fragment have at least 90% sequence identity. Claims 8 and 10-11 are rejected under this section 35 U.S.C. 112 because the claims are directed to a "genus" of polypeptides without any associated function. No description of identifying characteristics or functional characterization recognizing all of the sequences i.e., isolated polypeptide comprising a variant of a fragment of SEQ ID NO: 2, wherein the said fragment includes at least 200 consecutive amino acid residues of SEQ ID NO: 2 and wherein the variant and the said fragment have at least 90% sequence identity has been provided in the specification for the claims. The specification discloses the isolation of only a single polypeptide with the entire sequence of SEQ ID NO: 2 as having the calcineurin-like phosphoesterase activity encoded by the polynucleotide with SEQ ID NO: 1. No information, beyond the characterization of the polypeptide with SEQ ID NO: 2 having the calcineurin-like phosphoesterase activity have been provided by the applicants, which would indicate that they had possession of the claimed genus of the polypeptides. The specification does not contain any disclosure of the function of all the polypeptides within the scope of the claimed genus. The disclosed information is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus of polypeptides. Therefore, one skilled in the

art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed. Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

In response to the above rejection for written description, applicants have traversed arguing, that "claims 8-11 do indeed define a genus of polypeptides and do so strictly by reference to physical characteristics of the polypeptides, claim 8 comports fully with written description requirement of 35 U.S.C. 112 and claims 9-11 define inventions structurally by reference to variants of fragments of SEQ ID NO: 2, wherein the fragments have at least 90% or at least 95% sequence identity with each other...".

While it acknowledged that the current claims recite the genus of polypeptides in strictly structural terms, as discussed in the written description guidelines the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species, which are adequately described, are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. Satisfactory disclosure of a representative

number depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus, which embraces widely variant species, cannot be achieved by disclosing only one species within the genus. In the instant case the claimed genera of Claims 8, 10-11 includes species which are widely variant in function, amino acid sequences having at least 90% identity to any fragment of SEQ ID NO: 2, includes variants that encompass polypeptides **whose function or antigenecity may or may not be altered** (paragraphs 0040-0043, pages 9-10 of Specification). The genus of Claims 8, 10-11 is functionally diverse as it encompasses polypeptides with calcineurin-like phosphoesterase activity, those which lack such activity but are capable of inducing an antibody specific for one of SEQ ID NO: 2 as well as an enormous number of polypeptides with neither of these functions (lacking both calcineurin-like phosphoesterase activity or immunogenic), but possibly other undisclosed functions. As such, neither the description of the structure and function of SEQ ID NO: 2 nor the disclosure based solely on structural features present in all members of the genus is sufficient to be representative of the attributes and features of the entire genus. Therefore, examiner continues to maintain the rejection of claims 8, 10-11 under 35 U.S.C. 112, first paragraph, for written description

Claims 8 and 10-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polypeptide with SEQ ID NO: 2 having calcineurin-like phosphoesterase activity, does not reasonably provide enablement for polypeptide comprising a

variant of a fragment of SEQ ID NO: 2 or variant of a fragment of SEQ ID NO: 2, wherein the said fragment includes at least 200 consecutive amino acid residues of SEQ ID NO: 2 and wherein the variant and the said fragment have at least 90% sequence identity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with the claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 8 and 10-11 are so broad as to encompass any polypeptide comprising a fragment of SEQ ID NO: 2 or a variant of a fragment of SEQ ID NO: 2, wherein the said fragment includes at least 200 consecutive amino acid residues of SEQ ID NO: 2 and wherein the variant and the said fragment have at least 90% sequence identity. The scope of the claims are not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides broadly encompassed by the claims. Since the amino acid sequence of a protein encoded by a polynucleotide determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence and the respective codons in its polynucleotide, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed

knowledge of the ways in which the encoded proteins' structure relates to its function. However, in this case the disclosure is limited to amino acid sequence of only one calcineurin-like phosphoesterase i.e., SEQ ID NO: 2. It would require undue experimentation of the skilled artisan to make and use the claimed polypeptides. The specification is limited to teaching the making and using of SEQ ID NO: 2 as an calcineurin-like phosphoesterase, but provides no guidance with regard to the making of variants and mutants or with regard to other uses. In view of the great breadth of the claims, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While enzyme isolation techniques, recombinant and mutagenesis techniques are known, and it is routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions or deletions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any polypeptides comprising a fragment of SEQ ID NO: 2 or a variant of a fragment of SEQ ID NO: 2, wherein the said fragment includes at least 200 consecutive amino acid residues of SEQ ID NO: 2 and wherein the variant and the said fragment have at least 90% sequence identity, because the specification does not establish: (A) regions of the protein/polynucleotide structure which may be modified without affecting the activity of calcineurin-like phosphoesterase; (B) the general tolerance of the calcineurin-like phosphoesterase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue in the polypeptide with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including polypeptides with an enormous number of modifications. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of polypeptides having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

For enablement rejection, the applicants' cite: 1) the contemplated use of fragments (epitopes) of SEQ ID NO: 2 for raising antibodies, 2) that "the amino acid residues 47-211 of

CLPP1 are 91.3% identical to the consensus sequence of calcineurin-like phosphoesterase family and that similar portions of CLPP1 have significant homologies to other phosphatases" and 3) Fig.1 of the application provides an alignment of the consensus sequence of calcineurin-like phosphoesterase family with relevant residues of SEQ ID NO: 2.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. The claims are directed to a genus of polypeptides, fragments and variants which have 90%-95% sequence identity with SEQ ID NO: 2 with no associated function.

The specification does not contain any disclosure of the function of all polypeptide fragments comprising 200 consecutive amino acid residues of SEQ ID NO: 2 or any example to assert the function of full-length polypeptide comprising SEQ ID NO: 2, except for *in silico* analysis of the sequence (Examples 1-3), wherein the nucleic acid sequence of CLPPI is obtained from a newly genomic prediction pipeline and was performed as follows: "Briefly, the X-ray crystal structures of the catalytic domains of protein phosphatase were collected and aligned together according to their structural of identity/similarities. The alignment was converted into a "scoring matrix" which carried the structural profile of the phosphatase catalytic domains. This scoring matrix was then used to search the Celera Human Genome database for sequences that have phosphatase catalytic domains" and further performed BLAST analysis and hydrophobicity analysis to predict that SEQ ID NO: 2 as having calcineurin-like phosphoesterase activity (CLPP1).

It is well known in the art that sequence identity may not correlate with functional identity (For example: Melamine deaminase and Atrazine chlorohydrolase are two enzymes that exhibit 98% sequence identity but are functionally different; Seffernick et al., J Bacteriol. 183

(8): 2405-2410, 2001). No description of identifying characteristics or functional characterization recognizing all of the sequences i.e., polypeptides that have 90%-95% identity to SEQ ID NO: 2 has been provided in the specification for the claims. Therefore many functionally unrelated polypeptides are encompassed within the scope of these claims. Thus applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including polypeptides with an enormous number of modifications. The scope of the claims must bear a reasonable correlation with the scope of enablement and without sufficient guidance, determination of polypeptides having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. Therefore, examiner continues to maintain the rejection of claims 8, 10-11 under 35 U.S.C. 112, first paragraph, for enablement.

New- Claim Rejections: 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 8, 10-11 are rejected under 35 U.S.C. 102 (e) as being anticipated by Drmanac et al., (US PGPUB No.: US 2005/0196754 A1, claiming the priority date of US application

09/540,217, filed on 03/31/2000). Claims 8, 10-11 are drawn to a polypeptide comprising a fragment of SEQ ID NO: 2, wherein said fragment comprises at least 200 consecutive amino acids of SEQ ID NO: 2 or a variant of a fragment of SEQ ID NO: 2 wherein said fragment comprises at least 200 consecutive amino acid residues of SEQ ID NO: 2 and having 90%-95% sequence identity with SEQ ID NO: 2. Drmanac et al., (*supra*) disclose an isolated polypeptide sequence (Sequence 31948), which has 100% homology to the SEQ ID NO: 2 spanning from amino acid residues 57-266, a total of 210 consecutive amino acids. Therefore, Drmanac et al., anticipate claims 8, 10-11 as written (see copy of the sequence alignments provided).

Summary of Pending Issues

The following is a summary of issues pending in the instant application.

1) Claims 8, 10-11 are rejected under USC § 112, first paragraph, as failing to comply with the written description and enablement requirement.

2) Claims 8, 10-11 are rejected under USC § 102(e) as being anticipated by Drmanac et al., (US PGPUB No.: US 2005/0196754 A1, claiming the priority date of US application 09/540,217, filed on 03/31/2000), when given the broadest interpretation.

Conclusion

Claim 9 is objected to as being dependent upon a rejected base claim 8, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claims 8, 10-11 are rejected for the reasons identified in the Rejections and Summary sections of this Office Action. Applicants must respond to the

objections/rejections in each of the sections in this Office Action to be fully responsive for prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathirama Raghu whose telephone number is 571-272-4533. The examiner can normally be reached on 8 am - 5 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of the application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ganapathirama Raghu, Ph.D.
Patent Examiner
Art Unit 1652

July 26, 2006.

REBECCA E. PRUITT
PRIMARY EXAMINER
GROUP ~~1800~~ 1600